BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

B3

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/198, 31/44, 31/66, A61P 35/00, 17/06, 27/00, 9/10, 19/02, A61K 45/06 // (A61K 31/44, 31:195) (A61K 31/66, 31:195)

A1

(11) International Publication Number: WO 00/48591

(43) International Publication Date: 24 August 2000 (24.08.00)

(21) International Application Number: PCT/GB00/00511

(22) International Filing Date: 15 February 2000 (15.02.00)

(30) Priority Data:
9903404.3 16 February 1999 (16.02.99) GB

(71) Applicant *(for all designated States except US)*: ANGIOGENE PHARMACEUTICALS LTD. [GB/GB]; 14 Plowden Park, Aston Rowant, Watlington, Oxfordshire OX9 5SW (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DAVIS, Peter, David [GB/GB]; 10 Aston Park, Aston Rowant, Watlington OX9 5SW (GB).

(74) Agents: BAILLIE, Iain, C. et al.; Langner Parry, 52–54 High Holborn, London WC1V 6RR (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

(57) Abstract

Compositions for the inhibition of the formation of new vasculature by angiogenesis are provided comprising the combination of a vasculature damaging agent and an inhibitor of the formation or action of nitric oxide in mammalian systems. There are also provided the use of said combinations in medicaments and kits of said compounds and treatment employing said materials.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

This invention relates to a method for treating diseases involving active angiogenesis, to compositions useful for the treatment of diseases involving angiogenesis and to the use of the compositions in the preparation of a medicament for the treatment of diseases involving active angiogenesis. In one aspect of the invention the method involves the administration to a mammal of an inhibitor of nitric oxide in combination with a compound inducing vascular damage.

Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763, 1995). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.

Certain chemical compounds have been shown to have vascular damaging activity against the newly formed endothelium of solid tumours. These agents include, for example, combretastatin A4 phosphate (Dark et al., Cancer Research 57, 1829-1834, 1997), combretastain analogues (for example those described in J Med Chem 41, 3022-32,1998 by Ohsumi et al.), the flavone acetic acids, for example 5,6-dimethylxanthenone acetic acid (Zwi, Pathology, 26, 161-9, 1994), colchicine (Baguley et al. Eur J Cancer 27, 482-7, 1991). However some tumours are resistant to these agents.

One characteristic of tumours relatively resistant to vascular damaging agents is their ability to produce large amounts of nitric oxide. The role of nitric oxide in tumour

growth is unclear and there have been reports of both tumour-stimulating and tumour-inhibiting effects (Chinje and Stratford, Essays Biochem. 32, 61-72, 1997). It has been suggested that the antitumour effects of 5,6-dimethylxanthenone acetic acid are mediated in part by nitric oxide production (Thompsen et al. Cancer Chemother Pharmacol. 31,151-5, 1992).

We have found that the efficacy of vascular damaging agents can be improved by combining the treatment with inhibitors of the formation or action of nitric oxide in a mammalian system.

In particular the efficacy of vascular damaging agents can be improved by combination with inhibitors of nitric oxide synthases, the enzymes that produce nitric oxide from arginine. In particular the efficacy of vascular damaging agents against tumours relatively resistant to their effects is improved by treatment with a nitric oxide synthase inhibitor.

Accordingly in one aspect of the invention we provide a method of treatment for a mammal having a disease that involves active angiogenesis such method comprising the administration of a therapeutic or subtherapeutic amount of a vascular damaging agent together with an inhibitor of nitric oxide synthase in an amount sufficient to augment the effect of the vascular damaging agent. The method is useful for the treatment of diseases such as cancers, especially solid tumours, psoriasis, diabetic retinopathy, macular degeneration, atherosclerosis and rheumatoid arthritis.

The vascular damaging agent and the nitric oxide synthase inhibitor can be administered together or separately. The method may be used as a sole therapy or in combination with other treatments. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example

adriamycin and bleomycin; enzymes, for example aspariginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab; and anti-hormones for example tamoxifen. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

The vascular damaging agent and the nitric oxide synthase inhibitor can be administered by the same route or by different routes. Such routes of administration include oral, buccal, nasal, topical, rectal and parenteral administration. Each component of the method, the vascular damaging agent and the nitric oxide synthase inhibitor may independently be administered in a form suitable for the intended route of administration and such forms may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.
The preferred route of administration of each component will depend on the disease being treated. For solid tumours the components may each advantageously be delivered, either together or separately, as an intravenous infusion.

Vascular damaging agents are compounds which induce selective damage to newly formed, rather than established, vasculature. Many such compounds are known and it is considered this invention is generally applicable to such agents. Such agents include tubulin-binding agents, for example the combretastatins and their prodrugs, the colchinols and their prodrugs and (Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenylamine and its prodrugs, TNF-alpha inducing agents such as the xanthenone acetic acids, for example dimethylxanthenoneacetic acid, and antibodies targeted to the vasculature.

A wide variety of compounds which inhibit the formation or action of nitric oxide in mammalian systems can be employed. Specifically nitric oxide synthase inhibitors are those compounds which inhibit any of the forms of nitric oxide synthase. Such agents include derivatives of arginine, ornithine, lysine and citrulline, S-alkylthioureas and aminoguanidines. Where the nitric oxide synthase inhibitor is a derivative of arginine it may be, for example, an N^G-substituted L-arginine selected from N^G-nitro-L-arginine and alkyl esters thereof, N^G-methyl-L-arginine and N^G-amino-L-arginine. Where the nitric oxide synthase inhibitor is a derivative of ornithine it may be, for example L-N6-(1-iminoethyl)-ornithine. Where the nitric oxide synthase inhibitor is a derivative of lysine it may be, for example L-N6-(1-iminoethyl)-lysine. Where the nitric oxide synthase inhibitor is a derivative of citrulline it may be, for example L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline such as S-methyl-L-thiocitrulline.

In a further embodiment of the invention there is provided a composition for the treatment of diseases involving active angiogenesis. The composition of the invention comprises a vascular damaging agent in combination with a nitric oxide synthase inhibitor where both the vascular damaging agent and the nitric oxide synthase inhibitor are as hereinbefore defined.

Thus for example the composition may contain for example a combretastatin derivative, a colchicine derivative, a colchinol derivative, a xanthenone acetic acid derivative or a vascular targeted antibody, in combination with a nitric oxide synthase inhibitor for example a derivative of arginine, a derivative of ornithine, a derivative of lysine, a derivative of citrulline, a S-alkylthioureas or an aminoguanidine.

Particular examples of vascular damaging agents that may be present in the composition include combretastatin A4 and its prodrugs for example combretastatin A4 phosphate, (Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenylamine and its prodrugs, N-acetylcolchinol and its prodrugs for example N-acetylcolchinol-O-phosphate and 5,6-dimethylxanthenoneacetic acid.

Particular examples of nitric oxide synthase inhibitors which may be present in the composition include derivatives of arginine, ornithine, lysine and citrulline, S-alkylthioureas aminoguanidines and aminopyridines. Where the nitric oxide synthase inhibitor is a derivative of arginine it may be, for example, an N^G-substituted L-arginine selected from N^G-nitro-L-arginine and alkyl esters thereof, N^G-methyl-L-arginine and N^G-amino-L-arginine. Where the nitric oxide synthase inhibitor is a derivative of ornithine it may be, for example L-N6-(1-iminoethyl)-ornithine. Where the nitric oxide synthase inhibitor is a derivative of lysine it may be, for example L-N6-(1-iminoethyl)-lysine. Where the nitric oxide synthase inhibitor is a derivative of citrulline it may be, for example L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline such as S-methyl-L-thiocitrulline. Where the nitric oxide synthase inhibitor is an aminopyridine it may be for example 2-amino-4-methylpyridine.

The composition is useful for the treatment of diseases involving active angiogenesis for example solid tumours, psoriasis, diabetic retinopathy, macular degeneration, atherosclerosis and rheumatoid arthritis.

The relative proportion of each component will be determined by the identity of each individual vascular damaging agent or nitric oxide synthase inhibitor and by the disease to be treated.

The composition may include pharmaceutically acceptable excipients selected with regard to the intended route of administration and standard pharmaceutical practice. The composition may take a form suitable for oral, buccal, nasal, topical, rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the composition may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the identity of the individual components, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician and will depend on the particular vascular damaging agent and NO synthase inhibitor in the composition. However the dose of the vascular damaging agent envisaged is, for example, in the range 10-1000mg/m^2 body surface, preferably 20-200mg/ m^2 and that for the nitric oxide inhibitor 1-1000mg/m^2, preferably 5-500mg/ m^2. A unit dose form of the vascular damaging agent as, for example, a sterile solution for injection will usually contain, for example, 40-400mg of the active ingredient. A unit dose form of the nitric oxide synthase inhibitor as, for example, a sterile solution for injection will usually contain, for example, 10-1000mg of the active ingredient. A unit dose form of a composition containing both a vascular damaging agent and a nitric oxide synthase inhibitor as , for example, a sterile solution for injection will usually contain, for example, 40-400mg of the vascular damaging agent and 10-1000mg of the nitric oxide synthase inhibitor.

The composition of the invention may be administered as a sole therapy or in combination with other treatments. For the treatment of solid tumours the composition may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; enzymes, for example aspariginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab; and anti-hormones for example tamoxifen. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

In a further embodiment of the invention we provide the use of a compostion of the invention for the preparation of a medicament for the treatment of a disease involving active angiogenesis.

The invention will now be illustrated by the following Examples in which biological assays are used to illustrate the invention:

Induction of necrosis

Mice bearing either CaNT or SaS tumours were treated with the test compound and tumours excised after 24h, fixed in formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin. Sections were scored based on area of necrosis as follows:

% necrosis	score		% necrosis	score
0-10	1		51-60	6
11-20	2		61-70	7
21-30	3		71-80	8
31-40	4		81-90	9
41-50	5		91-100	10

Control tumours had mean scores of 2.0 (CaNT) and 1.0 (SaS).

EXAMPLE 1

In this assay the effect of a given dose of either a vascular damaging agent or a nitric oxide synthase inhibitor administered alone can be compared with the effect of a combination of the two agents.

Table 1: Enhancement of Combretastatin A4 phosphate (CA4P) activity in SaS tumours by coadministration of L-N^G-nitroarginine (L-NNA)

Treatment	Necrosis score ±SEM (n)
None	1.0±0 (10)
CA4P, 500mg/kg	1.7±0.7 (3)
L-NNA, 10mg/kg	2.0±1 (3)
CA4P, 500mg/kg + L-NNA 10mg/kg	9.0±0 (3)

EXAMPLE 2

Table 2: Enhancement of Combretastatin A4 phosphate (CA4P) activity in SaS tumours by coadministration of 2-amino-4-methylpyridine (AMP)

Treatment	Necrosis score ±SEM (n)
None	1.0±0 (10)
CA4P, 500mg/kg	1.7±0.7 (3)
AMP, 10mg/kg	1.0 (2)
CA4P, 500mg/kg + AMP 10mg/kg	4.5 (2)

EXAMPLE 3

Activity against tumour vasculature measured by fluorescent dye.

The following experiment further demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer 57, 247-253, 1988). The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after intra peritoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, 4, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels.

Table 3: Enhancement of Combretastatin A4 phosphate (CA4P) activity in CaNT tumours by coadministration of L-N^G-nitroarginine (L-NNA).

Treatment	Vascular Volume % ±SEM (n)
None	2.35
CA4P, 25mg/kg	1.03±0.14 (4)
L-NNA, 10mg/kg	2.45±0.04 (3)
CA4P, 25mg/kg + L-NNA 10mg/kg	0.63±0.25 (3)

CLAIMS:

1. A composition for the treatment of a disease involving active angiogenesis which comprises a vascular damaging agent together with an inhibitor of the formation or action of nitric oxide in a mammalian system.

2. A composition for the damage of the formation of new vasculature by angiogenesis comprising a combination of a vascular damaging agent and an amount of an inhibitor of nitric oxide synthase in an amount sufficient to augment the effect of the vascular damaging agent.

3. A composition according to claim 2 wherein said vascular damaging agent is selected from a tubulin-binding agent, a TNF-alpha inducing agent or an antibody targeted to vasculature.

4. A composition according to claims 2 and 3 wherein the nitric oxide synthase inhibitor is selected from a derivative of arginine, ornithine, lysine, citrulline, S-alkylthioureas or aminoguanidine.

5. A composition according to claim 4 wherein the nitric oxide synthase inhibitor is an N^G-substituted L-arginine selected from N^G-nitro–L-arginine and alkyl esters thereof, N^G-methyl-L-arginine and N^G-amino-L-arginine.

6. A composition according to claim 4 wherein the derivative of ornithine is L-N6-(1-iminoethyl)-ornithine.

7. A composition according to claim 4 wherein the derivative of lysine is L-N6-1-iminoethyl)-lysine.

8. A composition according to claim 4 wherein the derivative of citrulline is selected from L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline particularly S-methyl-L-thiocitrulline.

9. A composition according to any one of claims 1 to 8 which comprises also a pharmaceutically acceptable excipent appropriate to the method of administration.

10. A composition according to any one of claims 1 to 9 wherein the composition is in the form of a kit, one part of the kit containing the vascular damaging agent and the second part of the kit the nitric oxide inhibitor.

11. Use in the preparation of a medicament for the treatment of disease involving active angiogenesis and containing a vascular damaging agent characterised in that the medicament also contains an amount of an inhibitor of nitric oxide inhibitor sufficient to augment the effect of the vascular damaging agent.

12. A method of treatment for a mammal having a disease involving active angiogenesis said method comprising administration of a vascular damaging agent and an amount of an inhibitor of nitric oxide inhibitor sufficient to augment the effect of the vascular damaging agent.

13. A method according to claim 12 wherein the vascular damaging agent and nitric oxide inhibitor are administered substantially simultaneously but separately to the mammal under treatment.

14. Use of inhibitors of nitric oxide formation or action in the preparation of a medicament for augmentation of the effects of a vascular damaging agent.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 00/00511

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/198 A61K31/44 A61K31/66 A61P35/00 A61P17/06 A61P27/00 A61P9/10 A61P19/02 A61K45/06 //(A61K31/44, 31:195),(A61K31/66,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 09621 A (WELLCOME FOUND ;THOMSEN LINDY LOUISE (GB); KNOWLES RICHARD GRAHAM) 13 April 1995 (1995-04-13)	1-14
Y	page 2, line 9 -page 2, line 11 page 2, line 22 -page 2, line 26 claims 1,6,7	7,8
X	MOILANEN, E. ET AL: "Persistent induction of nitric oxide synthase in tumors from mice treated with the anti-tumor agent 5,6-dimethylxanthenone-4-acetic acid" BR. J. CANCER , vol. 77, no. 3, 1988, pages 426-433, XP000885438	1-14
Y	page 432, column 1, line 21 -page 432, column 2, line 2	7,8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 2000	25. 05. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Pilling, S

4

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int .tional Application No
PCT/GB 00/00511

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 30537 A (BEAMS RICHARD MANSFIELD ;DRYSDALE MARTIN JAMES (GB); HODSON HAROLD) 16 July 1998 (1998-07-16)	1-10,14
Y	abstract page 3, line 33 -page 4, line 2	7,8
X	WO 96 18617 A (MERCK & CO INC ;GUTHIKONDA RAVINDRA K (US); HAGMANN WILLIAM K (US)) 20 June 1996 (1996-06-20)	1-10,14
Y	abstract page 4, line 22 -page 4, line 26	7,8
X	WO 94 12165 A (WELLCOME FOUND ;GARVEY EDWARD PATRICK (US); TANOURY GERALD JOSEPH) 9 June 1994 (1994-06-09)	1-10,14
Y	abstract page 3, line 16 -page 3, line 20	7,8
Y	WO 95 01972 A (WISCONSIN MED COLLEGE INC) 19 January 1995 (1995-01-19) page 2, line 15 -page 2, line 19 page 7, line 21 -page 12, line 9	8
Y	WO 97 32585 A (LAI CHING SAN ;MEDINOX INC (US)) 12 September 1997 (1997-09-12) claim 16	7
A	CHAPLIN D.J. ET AL: "Modification of tumor blood flow: Current status and future directions." SEMINARS IN RADIATION ONCOLOGY, vol. 8, no. 3, 1998, page 151-163 XP000885557 the whole document	1-14

4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/00511

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-14 in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-14 in part

The present claims relate to compositions, uses and methods involving a combination of one group of functionally defined active agents with a further group of functionally defined active agents. Evidently each these functionally defined groups of compounds includes a large number of possible compounds resulting in many thousands of possible combinations.

It is further noted that in general the definition of compounds in terms of functional parameters makes a complete search impossible. In this regard, it is not always disclosed in the searched prior art documents whether candidate compound(s) would fulfill the requirements of such functional parameters or not.

Furthermore, in the present case it is considered that the definition of the "vascular damaging agent" as used in the claims is particularly unclear. This definition does not relate to a commonly recognized group of compounds nor does the description set out any clear objective way in which such agents may be identified. Similarly with reference to the definitions of the "inhibitor of the formation or action of nitric oxide" (see Claim 1) and "inhibitor of nitric oxide inhibitor" (see Claims 11 and 12), it is noted that the present specification only provides support for particular nitric oxide synthase inhibitors.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and supported by the present description and for which a search is feasible, namely combinations of (i) the particular vascular damaging agents which are identified in the description (see page 3 lines 25 to 32, page 4 lines 27 to 31 and the examples) with (ii) the particular nitric oxide synthase inhibitors which are identified in the description (see page 4 lines 1 to 13, page 5 lines 1 to 12 and the examples) and the general concept/idea underlying the invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ..tional Application No
PCT/GB 00/00511

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9509621	A	13-04-1995	AU	7787694 A	01-05-1995
			ZA	9407754 A	04-04-1996
WO 9830537	A	16-07-1998	AU	6208398 A	03-08-1998
			CZ	9902483 A	15-12-1999
			EP	0958277 A	24-11-1999
			NO	993429 A	12-07-1999
			PL	334368 A	28-02-2000
WO 9618617	A	20-06-1996	AU	4515896 A	03-07-1996
WO 9412165	A	09-06-1994	AU	5533094 A	22-06-1994
			CN	1095710 A	30-11-1994
			EP	0670720 A	13-09-1995
			JP	8503940 T	30-04-1996
			SI	9300616 A	30-06-1994
			ZA	9308867 A	26-05-1995
WO 9501972	A	19-01-1995	US	5424447 A	13-06-1995
			CA	2166222 A	19-01-1995
			EP	0707577 A	24-04-1996
			JP	8512318 T	24-12-1996
			US	5464858 A	07-11-1995
			US	5663364 A	02-09-1997
WO 9732585	A	12-09-1997	AU	2213197 A	22-09-1997
			AU	6998498 A	30-07-1998
			CA	2238029 A	12-09-1997